Clinical Observations after Radiotherapy with Re-Irradiation of Diffuse Intrinsic Pontine Glioma in Childhood - Clinical Case with Literature Review

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**ABSTRACT**

Diffuse intrinsic pontine glioma (DIPG) is an aggressive primary pediatric brain tumor. Despite the application of various curative methods, including radiotherapy (RT) with or without chemotherapy (Ch), targeted agents and immunological approaches, there is no achievement of clear improvement in median overall or progression-free survival (PFS).

We present a 6-year-old girl with DIPG after a 3 D conformal radiotherapy (3D CRT) in the brain stem tumor with a 1.5 cm insurance zone, by three fractions gradually rising daily doses (DD) 1.6 Gy -1.8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to total dose (TD) 33 Gy. The sum of total tumor dose is 38.6 Gy, corresponding to a biological equivalent dose to 2 Gy/ equieffective dose (EQD2) 46.71 Gy. After 8 months, due to local tumor progression, local tumor re-irradiation up to TD 20 Gy with DD 2 Gy was performed. In children with rapidly enhancing neurological symptoms and worsened forecast, it is appropriate to carry out hypophractionated RT up to 45 Gy with DD 3 Gy in 15 fractions, which achieves PFS similar to conventional fractionated RT.

Our observations from the realized RT are that despite highly risky tumor localization, hypofractionated RT is well tolerated, without acute neurological toxicity and allows second irradiation / re-irradiation, due to local tumor progression.

**Keywords**

Diffuse intrinsic pontine glioma, Childhood, Hypofractionated Radiotherapy, Re-irradiation, Progression-free survival.

**Introduction**

Diffuse intrinsic pontine glioma (DIPG) is the most aggressive primary pediatric brain tumor [1], which is diagnosed almost exclusively among children with a median age of 6 to 7 years [2-5]. A diagnosis of DIPG carries a dismal prognosis, with a 2-year survival rate of <10%, making this brain tumor one of the most fatal pediatric malignancies [6,7]. DIPG is an extremely aggressive brain tumor with the median survival <1 year, for which curative therapy is unavailable [8]. Most patients have a rapidly progressive and fatal course and usually die within 18 months after diagnosis [4]. Radiation therapy (RT) is considered an aggressive palliative therapy, because it prolongs survival by a mean of 3–6 months [9]. We present DIPG in a 6-year-old girl after hypofractionated RT, followed by re-irradiation due to local tumor progression, in order to discuss the clinical observations and the benefit of RT to improve overall and progression-free survival with good quality of life.

**Clinical Case**

We present a 6-year-old girl. In April 2021, the parents noticed speech and equilibrium difficulty, followed by subsequently headaches and episodic vomiting. On 14.05.2021, brain MRI was conducted, which visualized an infiltrate intraaxial lesion in the pontine brainstem, whose engaged structures were blended and...
The tumor has dimensions 44x33x34mm and high T2 signal intensity. A lightweight dilatation of both lateral ventricular and third cerebral ventricle without data on transependimal liquor resorption is recorded (Figure 1).

Figure 1: Brain MRI/14.05.2021 - An infiltrate intraaxial lesion in the pontine brainstem with high T2 signal intensity and dimensions 44x33x34mm.

After consultation with experienced neurosurgeons, it is considered diffuse infiltrative glioma in the pontine brainstem, which is inoperable and due to high risk, no biopsy is required. Oncology commission has assessed, that the only healing opportunity is to conduct a definitive radiotherapy (RT). In June / 2021, a 3D conformal radiotherapy (3D CRT) in the brain stem tumor with a 1.5 cm insurance zone, by three fractions gradually rising daily doses (DD) 1.6 Gy -1.8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to total dose (TD) 33 Gy was conducted. The sum of total tumor dose is 38.6 Gy, corresponding to a biological equivalent dose to 2 Gy/ equieffective dose (EQD2) 46.71 Gy. The child endured RT very well, without acute neurological effects and no changes in laboratory performance. Figure 2 and Figure 3 present tumor volume contouring for reparation of forthcoming RT and 3D CRT with dose tumor distribution and dose in adjacent normal brain structures.

Figure 2: 3D conformal radiotherapy planning raying by contouring of the brainstem tumor volume and the adjacent normal tissues and organs.

Figure 3: 3D Conformal Radiotherapy in the brainstem tumor by three fractions gradually rising DD 1.6 Gy -1.8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to TD 33 Gy/ biological equivalent dose to 2Gy/ equieffective dose (EQD2) 46.71 Gy. The histogram presents the distribution of radiation doses in the criticak adjacent normal tissues and in target volume.
After 8 months of completion of RT, a local tumor progression was established (Figure 4). Due to the lack of other alternative therapeutic methods, after a literary review, a re-irradiation was conducted. It was again Intensity modulated RT (IMRT) with VMAT technique in brain stem target volume with a 0.2 cm insurance zone with DD 2 Gy up tu TD 20 Gy (Figures 5,6). The child endured RT very well, without acute neurological effects and no changes in laboratory performance.

Figure 4: Brain MRI/ December 2021 Local tumor progression after 3D Conformal Radiotherapy with DD 1.6 Gy - 1.8 Gy - 2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to TD 33 Gy/ biological equivalent dose to 2 Gy/ equieffective dose (EQD2) 46.71 Gy.

Discussion
The brainstem is the posterior stalk-like part of the brain that connects the cerebrum with the spinal cord [10]. It has the critical roles of regulating cardiac and respiratory function, helping to control heart rate and breathing rate [11]. The pontine nuclei are a collection of pontine motor nuclei in the anterior pons that have many connections with the cerebellum via the middle cerebellar peduncle and assist with coordinating movement and help to modulate breathing [12]. Because of these important vital functions of the brain stem, the brain tumors localized therein are extremely difficult to treat, especially with the application of the radiation method, which can cause a sudden stopping of respiratory and cardiac activity.

Surgery of DIPG to relieve hydrocephalus, is not indicated, because the typical appearances on MRI are characteristic and reduction in tumour bulk only adds to the child’s worsened overall condition [13]. There is currently no indication for image guided stereotactic brain biopsy in children with a short history and typical MR appearances, because it currently will not alter management strategy [14]. During the past 3 decades numerous clinical trials have been conducted in newly diagnosed DIPG patients including radiotherapy with or without chemotherapy, targeted agents and immunological approaches. None of these trials have demonstrated a clear improvement in median overall or progression-free survival (PFS) [15]. Radiation remains the gold-standard treatment for diffuse intrinsic pontine gliomas (DIPG); by contrast, chemotherapy has not shown any benefit [16]. Several studies have concluded that conventional external-beam radiotherapy to a dose of 54 Gy in 30 fractions in 6 weeks is the mainstay of treatment [5,17-22] with median time to progression and overall survival of 6 and 9 months, respectively [21,23]. The current standard of treatment consists of conventionally fractionated RT to a range of 50.4–59.4 Gy in 28–33 fractions of 1.8 Gy daily, over 6 weeks, followed by the best supportive care [24]. Doses of radiation > 50 Gy are associated with improved survival compared with lower doses [25]. As a general principle, the treatment volume

Figure 5: Intensity modulated radiotherapy planning raying by contouring of the brainstem tumor volume and adjacent normal tissues and organs.
of the radiation field should encompass all the site(s) of disease with a defined margin to allow for non-imageable tumour spread into adjacent brain (1 cm for low grade and 2 cm for high grade tumours) [26]. To increase the overall and disease-free survival, other dose fractionation modes such as hyperfractionated and hypofractionated RT are applied [6,27]. Freeman et al. conducted a multiyear trial designed to assess the efficacy of sequentially escalated doses of hyperfractionated RT (66 Gy in 1.1 Gy fractions, 70.2 Gy in 1.17 Gy fractions, and 75.6 Gy in 1.26 Gy fractions; all twice daily in 60 fractions over 6 weeks) [28-30]. The conclusion is that, higher doses of hyperfractionated RT do not improve outcomes in DIPG. Given the paucity of data in favor of hyperfractionation schemes for DIPG, the potentially higher risks of acute toxicities, and the significant treatment burden associated with this approach [6]. Hypofractionated radiotherapy has potential radiobiological advantages over standard conventional fractionated therapy in newly diagnosed glioblastoma multiforme [31]. Some institutions have employed hypofractionated RT to decrease the length of therapy in an effort to reduce the patient's burden, with clinically similar levels of disease control reported [16,32-35]. In a retrospective study, Negretti et al./2011 treated with hypofractionated RT twenty-two children’s DIPG with rapid neurological worsening, linked to worse prognosis. Twenty patients received photon at a dose of 45 Gy in 15 fractions of 3 Gy and two children at a dose of 60 Gy and 45 Gy combined photon and neutron. The median OS was 7.6 months (range: 0.3–21.0) and median PFS was 5.7 months (range: 1.4–15.8) [16]. In the Jannsens G.O. et al/2013 study, 27 patients conducted hypofractionated RT over 3 to 4 weeks with either 39 Gy in three Gy fractions (n = 16) or 44.8 Gy in 2.8 Gy fractions (n = 11). No significant difference in median OS (9.0 vs 9.4 months; P = .8) and time to progression (5.0 vs 7.6 months; P = .2) was observed between hypofractionated versus conventional RT, respectively [32]. Hypofractionated radiotherapy is well tolerated with the advantage of decreasing the treatment burden on children and their families [6], with nearly comparable results to conventional fractionation, though not fulfilling the non-inferiority assumption [35]. Due to the shorter healing period of the hypofractionated RT, we considered to realize it after gradually rising daily doses due to critical neurological structures localized in the brain trunk (Figures 2,3). Despite our concerns about the tolerability of this irradiation, the child endured it very well without acute side neurological toxicity. Radiation therapy is essential in the definitive management of DIPG. With advances in treatment techniques, it is feasible to reinstate select patients with progressive disease [36]. Alvaro Lassaletta et al. identified 16 patients with progressive DIPG who received re-irradiation (rRT). Median time from diagnosis to progression was 10.5 months. rRT was given focially in 14 patients at a dose ranging from 21.6 to 36 Gy. All patients died, with a median time from rRT to death of 6.48 months. When compared to a historic cohort of 46 consecutive patients, the median time from progression to death was 92 days in the non-reirradiated patients versus 218 days in the reirradiated ones (P = 0.0001) [37]. ReRT can safely be delivered for progressive diffuse intrinsic pontine glioma. Utility analysis suggests that a regimen of 24 Gy in 12 fractions is preferred [38]. At first progression, 31 children with DIPG, aged 2-16 years, underwent re-irradiation (dose 19.8-30.0 Gy) alone (n = 16) or combined with systemic therapy (n = 15). An interval of ≥3 months after upfront radiotherapy was required before re-irradiation. Clinical improvement with re-irradiation was observed in 24/31 (77%) patients. On multivariable analysis, interval to progression (corrected hazard ratio = .27-.54; P < .01) and re-irradiation (corrected hazard ratio = .18-.22; P < .01) remained prognostic for survival [39]. Zamora PL et al /2021 identified five patients with progressive DIPG who received re-irradiation. Re-irradiation was well tolerated with no serious adverse events reported and all patients experiencing stable to improved neurologic function during treatment. Median overall survival from time of diagnosis was 16.3 months, which is longer than the historical average of less than 12 months. Re-irradiation (rRT) for symptomatic relief is an option at disease progression [40]. A Spanish group reported two patients with diffuse intrinsic pontine glioma (DIPG) who received a second re-irradiation course
at second tumor progression [41]. The second child received 39 Gy in 13 fractions followed by anti-angiogenic therapy. This was followed by 20 Gy in 10 fractions approximately 11 months later. Afterwards, Irinotecan and Rapamycin were given. Eight months later, a second re-irradiation course with 20 Gy in 10 fractions with concomitant Temozolomide was administered with good tolerance and rapid clinical response. Survival was 1 year after second re-irradiation. The cumulative EQD2 was equivalent to 89 Gy in this case [41]. Based on the attempt of the above-mentioned authors, in the presented clinical case with tumor progression after 8 months of the hypofractionated RT (Figure 4), we decided to carry out a re-irradiation in brain stem target volume with a 0.2 cm insurance zone with DD 2 Gy up to TD 20 Gy (Figures 5,6). Despite our concerns about the tolerability of this re-irradiation, the child experienced it very well without acute side neurological toxicity.

**Conclusion**

Diffuse intrinsic pontine glioma (DIPG) is the most aggressive primary pediatric brain tumor. Despite the various combined healing approaches, the forecast is extremely unfavorable. Inputs inability to carry out a biopsy, as well as partial tumor resection, the primary healing method is radiotherapy, applied by different fractionation of the radiation dose. In children with rapidly enhancing neurological symptoms and worsened forecast, it is appropriate to carry out hypofractionated RT up to 45 Gy with DD 3 Gy in 15 fractions, which achieves PFS similar to conventional fractionated RT. Our observations from realized RT are that despite highly risky tumor localization, hypofractionated RT is well tolerated, without acute neurological toxicity and allows second irradiation / re-irradiation, due to local tumor progression after 8 months. The preferred radiation dose of re-irradiation is TD 20 Gy with DD 2 Gy, which is well tolerated, improves neurological symptoms and increases the child's survival with good quality of life.

**References**


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